Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 1-6, 10-13, and 35-38 are pending in the application, with claim 1 being the independent claim. Claims 7-9, and 14-34 are sought to be cancelled without prejudice to or disclaimer of subject matter therein. Claims 1, 3, 4, 10 and 11 are sought to be amended. New claims 35-38 are sought to be added. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

I. Support for the Amendments

Support for the amendment to claim 1 and new claim 35 can be found in the specification, for example, at page 18, line 28 through page 19, line 1. Support for the amendment to claim 10 can be found in the specification, for example, at page 21, lines 3-19. Claims 3, 4 and 11 have been amended to correct typographical errors. Support for new claims 36 and 38 can be found in the specification, for example, at page 18, line 19 and at page 18, line 28 through page 19, line 2. Support for new claim 37 can be found in the specification, for example, at page 18, lines 15-18.

II. Claim Objections

The Examiner objected to claim 4 as being dependent upon a rejected base claim, *i.e.*, claim 1. The examiner stated that claim 4 would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. *See* Office Action at page 3. As discussed in detail below, Applicants traverse the rejection of claim 1 and request that the rejection be withdrawn. Accordingly, Applicants submit that the objection to claim 4 as being dependent upon a rejected base claim is moot and should also be withdrawn.

The Examiner objected to claims 1 and 11 for having two periods. *See* Office Action at page 3. Applicants have amended claims 1 and 11 such that the designation "Seq. ID No." has been replaced with "SEQ ID NO:" Accordingly, the objection to claims 1 and 11 for having two periods has been fully addressed and should be withdrawn.

The Examiner objected to claim 3 because the word "virion" was inadvertently misspelled. *See* Office Action at page 3. Applicants have amended claims 3 such that "virion" is now spelled correctly. Accordingly, the objection to claim 3 has been fully addressed and should be withdrawn.

III. Rejection under 35 U.S.C. § 112, Written Description

The Examiner rejected claim 1 under 35 U.S.C. § 112, first paragraph, as allegedly unpatentable for lack of written description. Applicants respectfully traverse the rejection.

The Examiner stated "the specification does not provide sufficient description of a genus of polynucleotide sequences that possess any of the biological characteristics of Seq ID No:1." Office Action, page 4, lines 1-2. Applicants respectfully disagree.

According to the *Written Description Guidelines*, Federal Register Vol. 66, No. 4:1099-1107:

> [a]n applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, *i.e*, complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of the characteristics.

Federal Register Vol. 66, No. 4, page 1106. Thus, the guidelines indicate that a representative species may be adequately described through its structure, through its functional characteristics, or through a combination of structure and function.

Amended claim 1 recites a DNA construct that comprises, *inter alia*, a DNA molecule of SEQ ID NO:1 or a DNA molecule which is at least 40% homologous thereto, or a fragment thereof, and wherein said DNA molecule codes for a protein that has an activity of AD7c-NTP. The structure and functions of AD7c-NTP are described throughout the specification, for example, at page 17, lines 18-26; at page 18, line 28 through page 19, line 2; and at page 34, line 6 through page 35, line 15. Thus, description of both the structure and the function of the representative species has been provided throughout the specification.

The written description requirement serves to ensure that the inventor had possession, as of the filing date, of the claimed invention. The Examiner stated that "[p]ossession may be shown by an actual reduction to practice, clear depiction of the invention in a detailed drawing, or by *describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the*

inventor had possession of the claimed invention." Office Action, page 4, lines 18-20 (emphasis added, case citation omitted).

One of ordinary skill in the art would know how to generate DNA molecules that share 40% homology with another DNA molecule. The information provided in the specification would allow one of ordinary skill in the art to determine and identify which DNA molecules that have an activity of AD7c-NTP. For example, Examples 8 and 10 of the specification describe assays that can be used to identify functional characteristics associated with the AD7c-NTP protein. "These studies demonstrate that over expression of AD7c-NTP in transfected neuronal cells promotes neuritic sprouting and cell death . . . ." *See* specification, page 46, lines 21-23.

The functional and structural characteristics described in the specification provide guidance to one of ordinary skill in the art as to which DNA molecules are members of the claimed genus. Therefore, one skilled in the art would recognize that Applicants were in possession of the claimed genus, and thus, Applicants respectfully request that the rejection be withdrawn.

IV. Rejection Under 35 U.S.C. § 112, Enablement

The Examiner rejected claims 1-6 and 10-13 under 35 U.S.C. § 112, first paragraph, allegedly for lack of enablement. Applicants respectfully traverse this rejection.

The Examiner stated:

> Since, the relationship between a sequence of a peptide and its tertiary structure (i.e. its activity) are not well understood and are not predictable [citation omitted], it would required [sic] undue experimentation for one skilled in the art to arrive

> at other polynucleotides sequences that have Seq ID No:1 activity.

Office Action, page 7, lines 7-10. Applicants respectfully disagree.

Amended claim 1 recites a DNA construct that comprises, *inter alia*, a DNA molecule of SEQ ID NO:1 or a DNA molecule that is at least 40% homologous thereto, or a fragment thereof, and wherein said DNA molecule codes for a protein that has an activity of AD7c-NTP. Undue experimentation would not be required to generate DNA molecules that are at least 40% homologous to SEQ ID NO:1 and encode for a protein that has an activity of AD7c-NTP. As discussed *supra*, one of ordinary skill in the art would be able to generate DNA sequences with 40 percent identity to SEQ ID NO:1. Further, the specification provides information and working examples for how to identify the DNA molecules that possess an activity of AD7c-NTP.

At pages 45-46 and pages 48-50 of the specification, assays are described that can be used to identify DNA molecules that encode for proteins that possess an activity of AD7c-NTP. The described assays involve only routine experimentation, and all of the methods are well known in the art. Nothing more than routine molecular biology techniques are required to identify members of the claimed genus. Given the level of skill of the ordinary artisan, identifying members of the claimed genus, in light of the specification, would be trivial. Therefore, Applicants respectfully request that the rejection be withdrawn.

The Examiner stated:

> In addition, claim 5 and claims dependent thereof [sic], as best understood, are readable on an in vitro and in vivo host cell transformed with the DNA construct, which comprises a DNA molecule of Seq ID No:1 or a DNA molecule which is at least 40% homologous thereto, or a fragment thereof;

> wherein said DNA molecule is under control of a heterologous neuro-specific promoter is not enabled.

Office Action, at page 7, last paragraph through page 8. Applicants respectfully traverse this rejection.

The initial burden of proving that a specification is non-enabling is on the Examiner. *See In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). It is axiomatic that a specification is presumed to be enabling unless the Examiner provides acceptable objective evidence or sound scientific reasoning that shows it would require undue experimentation for one of ordinary skill in the art to make and use the claimed invention. *See In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971). Here, the Examiner has failed to provide any objective evidence to substantiate the allegation of non-enablement.

In an attempt to validate the allegation of non-enablement, the Examiner cites the publication of Anderson *et al.*, Nature, Vol. 392, pp. 25-30, 1998, and the publication of Verma *et al.*, *Nature*, Vol. 389, pp. 239-242, 1997. Both articles are review articles that discuss the promises and prospects of gene therapy. However, these articles present no original data and merely represent the opinions of the authors. The Examiner fails to consider other studies that have presented positive data with respect to gene therapy.

For example, Boviatsis *et al.*, *Cancer Research* 54:5745-5751 (1994) (copy attached herewith as *Exhibit 1*), entitled "Long-term Survival of Rats Harboring Brain Neoplasms Treated With Ganciclovir and a Herpes Simplex Virus Vector That Retains an Intact Thymidine Kinase Gene," demonstrated that a Herpes Simplex virus vector could be

used to deliver the thymidine kinase gene, and increase the long term survival of rats with gliosarcoma tumors.

Furthermore, Tamiya *et al.*, *Gene Therapy* 2:531-538 (1995) (copy attached herewith as *Exhibit 2*), entitled "Transgene Inheritance and Retroviral Infection Contribute to the Efficiency of Gene Expression In Solid Tumors Inoculated With Retroviral Vector Producer Cells," demonstrated that a marker gene, *lacZ*, could be delivered *in vivo* into an established C6 glioma in nude mice, using a retroviral vector. This study demonstrates that *in vivo* delivery of a transgene can be successful.

The Examiner stated "one skilled in the art would have to engage in a large quantity of experimentation in order to practice the claimed invention based on the applicant's disclosure and the unpredictability of gene therapy." Office Action, at page 10. However, some experimentation is permitted as long as it is not "undue." *See In re Angstadt*, 190 USPQ 214, 219 (CCPA 1976).

In determining whether undue experimentation would be required to practice a claimed invention, several relevant factors have been identified. These factors include: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. *See In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Thus, whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations.

At page 8 of the Office Action, the Examiner summarized the issues involved in a DNA therapy protocol. None of the issues presented by the Examiner require "undue" experimentation. Given the level of skill in the art, it would require only routine molecular biology protocols to determine the type of vector and the amount of DNA to be administered, the rate of degradation of the DNA, the level of the mRNA produced, and the amount and the stability of the protein product.

According to Anderson *et al.*, "[m]ore than 300 clinical protocols have been approved worldwide and over 3,000 patients have carried genetically engineered cells in their body." Anderson *et al.*, page 26, first paragraph. From these 300 clinical protocols, one of ordinary skill in the art would be able to identify the appropriate routes and time courses of administration. Experimentation is required but the state of the prior art provides significant guideposts to help the average artisan find the most appropriate route of administration.

The Examiner's statement regarding the "unpredictability of gene therapy" is based on out of date review articles that give only a cursory overview of the gene therapy field. The review articles fail to mention several studies that demonstrate the efficacy of *in vivo* gene therapy. Applicants submit that the Examiner has not presented any probative, objective evidence or scientific reasoning to substantiate the allegation of non-enablement. Therefore, Applicants respectfully request that this rejection be withdrawn.

V. Rejections under 35 U.S.C. § 112, Second Paragraph

The Examiner rejected claim 10 allegedly because there is insufficient antecedent basis for the limitation "protein coded for by the DNA construct." Applicants traverse this

rejection. However, in an effort to expedite prosecution, Applicants have amended claim 10 to recite "protein coded for by the DNA construct of said host cell." The host cell contains a DNA construct, which comprises a DNA molecule of SEQ ID NO:1 or a DNA molecule that is at least 40% homologous thereto, wherein said DNA molecule codes for a protein having an activity of AD7c-NTP. One of ordinary skill in the art would clearly understand that the DNA construct is the DNA construct defined by claim 1. Thus, the Examiner's rejection has been rendered moot.

The Examiner rejected claims 11 and 12 allegedly because there is insufficient basis for the limitation "said protein." The Examiner stated "[i]t is not apparent what protein is being overexpressed since the base claim (claim 1) comprises a DNA molecule of Seq ID No:1 and/or possibly another protein." Office Action, at page 11. Applicants respectfully traverse this rejection.

Applicants respectfully point out that claim 1 recites, *inter alia*, "DNA construct, which comprises a DNA molecule of SEQ ID NO:1 or a DNA molecule which is at least 40% homologous thereto, or a fragment thereof." The use of the conjunction "or" means that the DNA construct contains either a DNA molecule of SEQ ID NO:1 or a DNA molecule which is at least 40% homologous thereto, or a fragment thereof. There is no ambiguity in this language.

Claim 12 recites "wherein said protein is over-expressed by said host cell." Claim 12 ultimately depends from amended claim 1. One of ordinary skill in the art would understand that the over-expressed protein is the protein coded for by the DNA construct of claim 1, which is either a DNA molecule of SEQ ID NO:1 or a DNA molecule that is at least

40% homologous thereto, or a fragment thereof. Applicants request that this rejection be withdrawn.

The Examiner stated "[i]t is not apparent what protein has Seq ID No: 2 in claim 11." Office Action, at page 11. Claim 11 ultimately depends from amended claim 1, which recites, *inter alia*, a DNA construct, which comprises a DNA molecule of SEQ ID NO:1 or a DNA molecule that is at least 40% homologous thereto, wherein said DNA molecule codes for a protein having an activity of AD7c-NTP. Applicants direct the Examiner's attention to page 18, line 19 of the specification, which reads "[p]referably, the DNA construct encodes AD7c-NTP having Seq ID No.2." It would be clear to one of ordinary skill in the art that SEQ ID NO:2 is the amino acid sequence of the protein AD7c-NTP. Thus, Applicants respectfully request that this rejection be withdrawn.

VI. Other Matters, Information Disclosure Statement

At page 2 of the Office Action, the Examiner indicated that the Information Disclosure Statement (IDS) filed on February 14, 2000 does not fully comply with the requirements of 37 C.F.R. § 1.98. Applicants request clarification about this matter as Applicants did not file an IDS on February 14, 2000.

The Examiner also indicated that the IDS filed on December 3, 1999 is missing. However, the PTO 1449 Forms that the Examiner has initialed and returned with the present Office Action cites all of the documents that were cited in the IDS filed on December 3, 1999. Thus, Applicants believe all of the documents cited in the IDS filed on December 3,1999 have been considered by the Examiner. If the pleading styled "Information Disclosure Statement" filed December 3, 1999, is missing in the file, Applicants respectfully

request that the Examiner so inform Applicants in the next action so that a copy may be filed.

At page 2 of the Office Action, the Examiner indicated that articles AS5-AT6 from the PTO 1449 Forms filed on January 2, 2001 are missing. Applicants submit herewith a copy of the PTO 1449 Forms and a copy of articles AS5-AT6, which were filed on January 2, 2001.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

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Version with markings to show changes made

In the specification:

Please insert the following paragraph at page 1, after the title:

CROSS-REFERENCE TO RELATED APPLICATIONS

This is a 371 of PCT/US98/03685, filed February 26, 1998, published in English on September 3, 1998, which claims the benefit of U.S. Provisional Application 60/038,908, filed February 26, 1997.

In the claims:

Please cancel claims 7-9 and 14-34.

Please substitute the following claim 1 for the pending claim 1:

1. (Once amended) A DNA construct, which comprises a DNA molecule of [Seq. ID No. 1] SEQ ID NO:1 or a DNA molecule which is at least 40% homologous thereto, or a fragment thereof, wherein said DNA molecule is under control of a heterologous neuro-specific promoter, and wherein said DNA molecule codes for a protein that has an activity of AD7c-NTP when expressed in neuronal cells.

Please substitute the following claim 3 for the pending claim 3:

3. (Once amended) The DNA construct of claim 1, which is contained by a [viron] virion.

Please substitute the following claim 4 for the pending claim 4:

4. (Once amended) The DNA construct of claim 1, wherein said DNA molecule has [Seq. ID No. 1] SEQ ID NO:1.

Please substitute the following claim 10 for the pending claim 10:

10. (Once Amended) An *in vitro* method for screening a candidate drug that is potentially useful for the treatment or prevention of Alzheimer's disease, neuroectodermal tumors, malignant astrocytomas, and glioblastomas, which comprises:

(a) contacting a candidate drug with the host cell [line] of claim 5, and

(b) detecting at least one of the following:

(i) the suppression or prevention of expression of the protein coded for by the DNA construct of said host cell;

(ii) the increased degradation of the protein coded for by the DNA construct ~~of said host cell~~; or

(iii) the reduction of frequency of at least one of neuritic sprouting, nerve cell death, degenerating neurons, neurofibrillary tangles, or irregular swollen neurites and axons in the host;

due to the drug candidate compared to a control cell line which has not contacted the candidate drug.

Please substitute the following claim 11 for the pending claim 11:

11. (Once amended) The method of claim 10, wherein said protein has [Seq. ID No. 2] SEQ ID NO:2.

Please add new claims 35-38.